Original article

Title: Intraoperative Dexmedetomidine Infusion might preserve Cognitive Functions of Elderly patients undergoing Spinal Surgeries under General Anesthesia.

Running Title: Dexmedetomidine preserves Cognitive Functions of Elderly patients.

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Abstract

Background: Elderly patients are more vulnerable to anesthesia-related cognitive dysfunction. Spinal surgery consumes long theater time that may affect patients' outcome especially the elderly ones. Anesthetic manipulations were supposed to modulate cognitive outcomes of patients.

Objectives: Evaluation of the effect of intraoperative (IO) dexmedetomidine (DEX) infusion during spinal surgery on the incidence and severity of postoperative cognitive disorders (POCD).

Patients & Methods: 152 patients were divided into Group P received placebo infusion and Group D DEX infusion (0.5 µg/kg/h) with induction of anesthesia until wound closure. Cognitive function (CF) was assessed using Mini-Mental State Examination (MMSE) pre- and postoperatively. The median value of CF deficit in 4-wk PO was calculated and its correlation to type of IO infusions and patients' data was evaluated. The effect of DEX infusion on the incidence and severity of POCD is the study outcome.

Results: DEX infusion significantly decreased the incidence and severity of POCD with significantly lower deficit in MMSE score of patients of group D. The MMES deficit was positively correlated to age, body mass index (BMI), presence of systemic diseases and infusion type. The use of DEX, young age, and low BMI are significant predictors for normal CF.

Conclusion: DEX infusion for elderly patients undergoing major surgeries of long operative time and predicted blood loss significantly reduced the incidence and severity of POCD. The used dose of DEX was appropriate for preserving CF without hemodynamic effects.

Keywords: Postoperative cognition function, Dexmedetomidine, Elderly patients, Spinal surgery

Introduction

Postoperative cognitive dysfunction (POCD) is one of the main causes of morbidity after major surgery and its pathogenesis is multifactorial and underlying pathogenic mechanisms are still unclear [(1)]. Some precipitating factors are modifiable, especially alcohol consumption, smoking, blood pressure and glycemic control, and duration of surgery [(2)]. Anesthesia-related factors such as anesthetic agents and drugs, duration of ventilation, early detection, and management are also modifiable [(3)]. The non-modifiable factors are multiple especially old age, type of surgery; cardiac or non-cardiac [(1)], preoperative low cognitive function (CF) [(4)], gender, pre-existing cerebrovascular, neurological conditions, renal and hepatic impairment, emergency surgeries, and environmental changes [(3)].

Dexmedetomidine (DEX) is a selective α_2-adrenaline receptor agonist with a dose-dependent sedative, minimal depressive effects, and analgesic effect through the inhibition of pain signals [(5)]. DEX exerts a cardioprotective effect during early and late reperfusion phases through mitochondrial K-channels and mBKCa-channels, respectively [(6)]. Also, DEX pretreatment attenuates myocardial ischemia-reperfusion injury-induced acute kidney injury by relieving the endoplasmic reticulum stress [(7)]. DEX was found to have neuroprotective effects against ischemia-reperfusion damage [(8)], traumatic brain injury [(9)], and neurotoxicity caused by anesthetic agents such as propofol [(10)].

Hypothesis

This study supposed the use of DEX infusion during surgery may lessens or ameliorate the effects of surgery and/or anesthesia on the CF and thus may act as a type of prophylaxis

Objectives

The study tried to assess the effects of intraoperative DEX infusion on the incidence and severity of POCD in patients undergoing spinal surgery

Design

Prospective double-blinded randomized placebo-controlled clinical trial

Setting

Anesthesia, Pain & ICU department, Faculty of Medicine, Benha University and multiple private neurosurgical centers

Ethical Consideration

The study was started in Aug 2019 after obtaining the preliminary approval of the study protocol by the Local Ethical Committee at Benha Faculty of Medicine and the final approval was obtained after the completion of case collection by approval number RC:4.1.2022. The study protocol was discussed with each patient and those who accepted to participate in the study signed written consent.

Patients & Methods

All patients assigned for spinal discectomy and vertebral fixation were clinically evaluated for collection of demographic and clinical data and given blood samples for routine laboratory investigations.

Inclusion criteria

Patients of ASA grade I-III, assigned for lumbar discectomy and spinal fixation and were free of exclusion criteria were included in the study.

Exclusion criteria

Age older than 75 years to guard against the effect of senility on the CF, ASA grade IV, maintenance on drugs affecting CF especially hypnotics, alcohol addiction, allergy to the drugs to be used, presence of neurological diseases, psychiatric disorders, or refusal to participate in the study are the exclusion criteria.

Sample size calculation

Previous studies had reported an incidence of POCD ranging between 26.1% [(11)] and 42.2% [(12)] in patients who underwent non-cardiac variant surgical procedures, so it was supposed that the predicted incidence with placebo will be in this range, but DEX infusion was predicted to reduce this incidence down to 15%. The calculated sample size to attain a study power of 80% with α value of 0.05 and β value of 0.2 is 72 patients per group.

Randomization and Grouping

Patients were randomly divided into two groups using a computer-generated sequence with 1:1 blocks; Group P received unlabeled plain normal saline (0.9NaCl) and Group D received unlabeled normal saline (0.9% NaCl) to which DEX was added to provide 0.5 µg/kg/h. Infusions were started with induction of anesthesia until wound closure.

Anesthetic technique

Anesthesia was induced with propofol (1.5 mg/kg), fentanyl (2 µg/kg), and atracurium (0.5 mg/kg) and was maintained by isoflurane inhalation (1.2 MAC) and fentanyl 1 µg/kg/hour was used as intraoperative analgesia. Preoperative and intraoperative monitoring for heart rate, systolic, diastolic, mean arterial blood pressure (MAP), and oxygen saturation were conducted non-invasively. Intraoperative bradycardia and hypotension were defined as heart rate <60 beats/min, and MAP <65 mmHg and were treated with IV atropine or ephedrine [(13)].

Evaluation of Cognition Function (CF)

Cognitive function was assessed preoperatively, 48-hr, 1-wk, 2-wk and 4-wk PO using the Mini-Mental State Examination (MMSE), which is a 30-point questionnaire (Appendix 1) and lower scores indicated cognitive dysfunction (CD) and a score = 25-30 indicates normal CF [(14)].

Study outcome

The study primary of the study is the effect of DEX intraoperative infusion on the incidence and severity of POCD. The secondary outcome is defining the best predictor for the change in CF.

Statistical analysis

The median values of PO deficit in 4-wk MMES scores in comparison to preoperative scores were calculated and statistical significance was assessed using the Mann-Whitney test. Inter-group comparisons using the one-way ANOVA test. Non-parametric data were compared using the Chi-square test. Pearson's correlation was used to assess the relation between PO deficit in MMSE and patients' data and the used IO infusion. Predictors for the possibility of development of POCD among patients' data were defined using the Receiver characteristic curve (ROC) and the Multivariate Regression analyses. Statistical analysis was conducted using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

During the study duration, 152 patients were randomly divided into two equal groups (Fig. 1) after exclusion of 12 patients; 3 had associated kyphosis, 4 patients were maintained on antifibrinolytic after previous cardiac surgery, two patients had previous cerebrovascular stroke, two patients were found to have vertebral patches simulating metastatic lesions and one refused to sign the consent. Preoperative and intraoperative data of the studied patients showed non-significant differences, apart from operative blood loss and need for blood transfusion that was significantly decreased with DEX infusion in comparison to placebo (Tables 1 and 2).

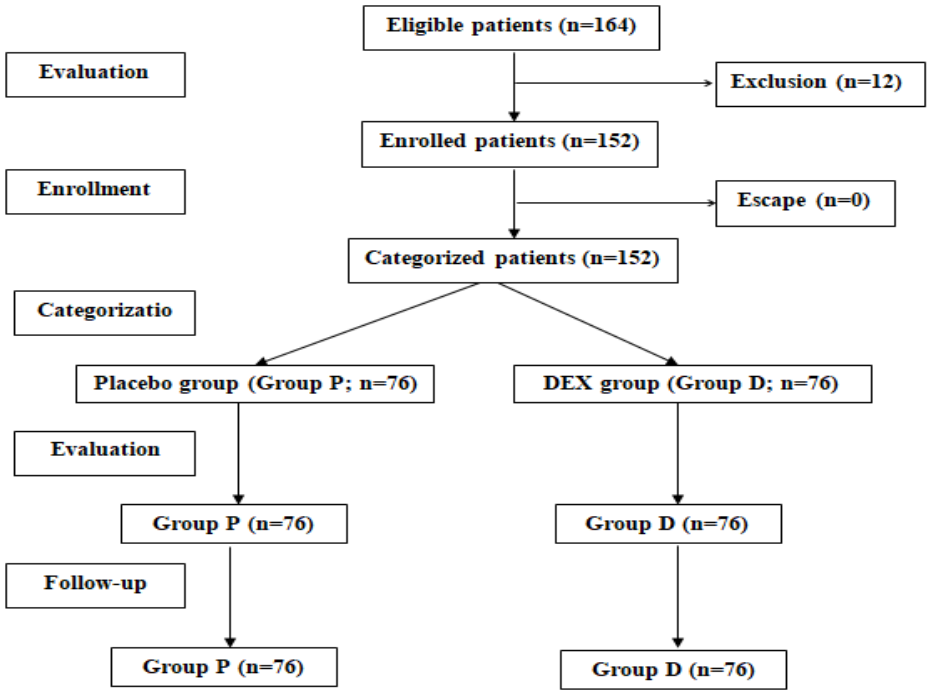

Fig. (1): Study Flow Chart

Table (1): Preoperative and Intraoperative data of patients of both groups

Data			Group P (n=76)	Group D (n=76)
Age (years)			60.3 (±9.1)	58.1 (±8.8)
Body mass index (kg/m^2)			31.1 (±4.1)	30.5 (±3.9)
Sex; Male: Female			46:30	51:25
Educational levels	Illiterate		15 (19.7%)	13 (17.2%)
	Primary school		22 (28.9%)	26 (34.2%)
	Secondary school		23 (30.3%)	20 (26.3%)
	High institute		6 (7.9%)	8 (10.5%)
	College Graduate		10 (13.2%)	9 (11.8%)
Employee			55 (72.4%)	58 (76.3%)
Systemic diseases	Diabetes mellitus		13 (17.1%)	16 (21%)
	Hypertension		11 (14.5%)	13 (17.2%)
ASA grade	I:II: III		13:47:16	10:54:12
Heart rate (beat/min)		Baseline	76.9±9.1	78.8±7.2
		End of surgery	75.3±5.5	77±6.9
Mean arterial pressure (mmHg)		Baseline	85.9±5.4	84.6±5.1
		End of surgery	84.5±6.8	82.6±7.6
Operative time (min)			158.2±13.3	162.5±15.2
Blood loss (ml)			556±144.7	505±142.8*
Frequency of blood transfusion			12 (15.8%)	4 (5.3%)*

Data are presented as mean; standard deviation, numbers & percentages; * indicates a significant difference at P<0.05

All patients had normal preoperative CF with a non-significant difference between both groups. During PO follow-up, 37 (24.3%), 51 (33.6%), 75 (49.3%), and 117 (77%) patients had normal CF, at 48-hr, 1, 2, and 4 weeks, respectively with a significantly higher frequency of patients had normal CF among patients of group D at 2-wk (P=0.006) and 4-wk (P<0.001). The determined MMSE score progressively increased from 48-hr PO evaluation till the last evaluation at the 4-wk PO with significantly (P<0.001) higher scores for patients of group D than those of group P (Table 2, Fig. 2).

Table (2): Postoperative evaluation of the cognitive function of patients of both groups using the Mini-Mental State Examination

		Group P (n=76)	Group D (n=76)
Preoperative score		29.5±0.89	29.3±1.1
48-hr PO	Normal	14 (18.4%)	23 (30.3%)
	Mild CD	25 (32.9%)	41 (53.9%)
	Moderate CD	37 (48.7%)	12 (15.8%)
	Score	20.7±4	23.5±3.7†
1-wk PO	Normal	20 (26.3%)	31 (40.8%)
	Mild CD	23 (30.3%)	35 (46%)
	Moderate CD	33 (43.4%)	10 (13.2%)
	Score	22.2±4	25±3.6†
2-wk PO	Normal	29 (38.2%)	46 (60.6%)
	Mild CD	30 (39.5%)	27 (35.5%)
	Moderate CD	17 (22.3%)	3 (3.9%)
	Score	23.9±3.9	26.9±3†
4-wk PO	Normal	46 (60.5%)	71 (93.4%)
	Mild CD	18 (23.7%)	5 (6.6%)
	Moderate CD	12 (15.8%)	0
	Score	25.7±3.8	28.6±1.7†

Data are presented as mean; standard deviation, numbers & percentages; * indicates a significant difference at P<0.001

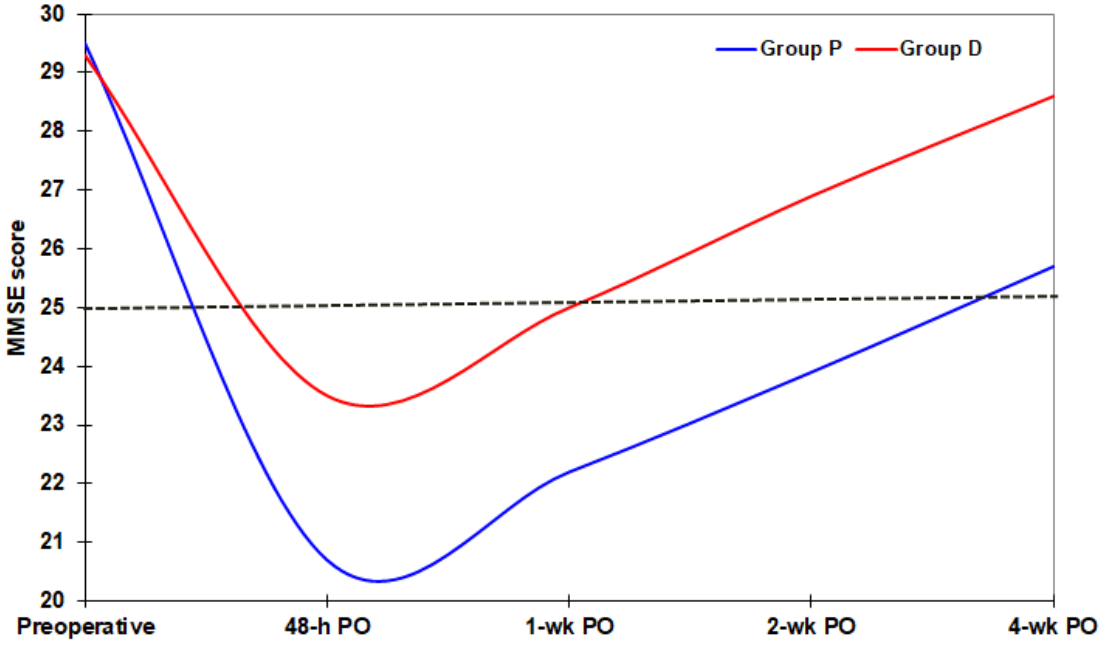

Fig. (2): Mean value of MMSE score of cognitive function determined follow-up of patients of both groups (Dashed line indicates normal level)

The calculated MMSE deficit between preoperative and 4-wk PO MMSE was significantly lower in patients of group D (0; range: 0-5) than in patients of group P (3; range: 0-11). The calculated deficit was positively correlated with the use of placebo (r=0.537, P<0.001), older patients' age (r=0.375, p<0.001), higher BMI (r=0.279, p=0.001) and presence of systemic diseases (r=0.287, p<0.001). The ROC curve analysis defined the use of DEX, age, BMI, educational level, and presence of systemic diseases as the significant preoperative predictors for the development of POCD (Table 3, Fig. 3), and Regression analysis determined the use of placebo and

older age as the most significant (P<0.001) predictors for development of POCD with β=0.480 and 0.290, respectively.

Table (3): ROC curve analysis of patients' preoperative data and the use of DEX as predictors for the possibility of development of POCD

Variables	The area under the curve	Standard error	p	95% Confidence interval
Use of DEX	0.718	0.043	<0.001	0.634-0.802
Age	0.281	0.041	<0.001	0.201-0.360
BMI	0.337	0.045	0.001	0.249-0.425
Gender	0.506	0.048	0.902	0.412-0.600
Educational level	0.605	0.047	0.028	0.514-0.696
Employment	0.526	0.048	0.587	0.433-0.619
Systemic disease	0.384	0.045	0.015	0.295-0.473
ASA grade	0.433	0.047	0.163	0.341-0.526

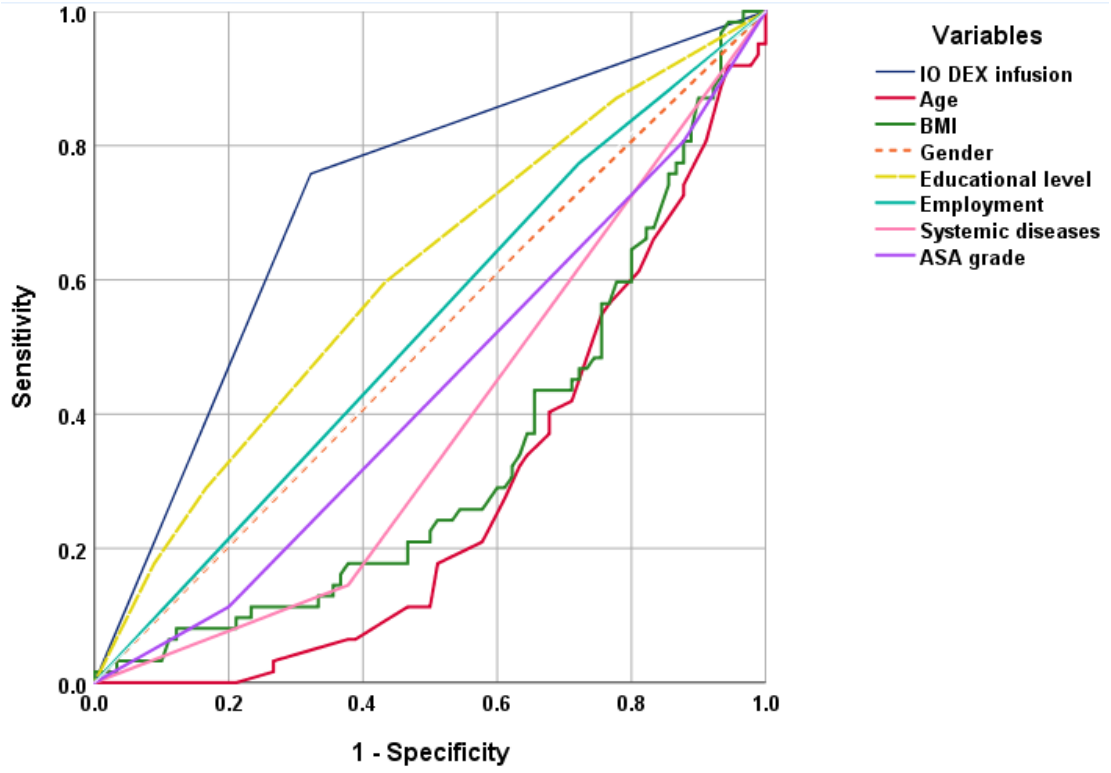

Fig. (3): ROC analysis of preoperative patients' data and the use of DEX intraoperative infusion as predictors for the development of POCD

Discussion

Postoperative cognitive dysfunction (POCD) is a common event that was reported in 47 patients with an incidence of 42.1%. Such a figure coincided with that recently reported after anesthesia for various non-cardiac surgeries [13, 15-18]. However, the used DEX infusion starting with induction of anesthesia till wound closure significantly reduced the incidence and severity of POCD. Moreover, patients who received DEX infusion and developed CD regained their normal CF significantly faster and by the end of 4-wk PO, only 5 patients had mild CD, while among those who received placebo infusion 30 patients (18 mild and 12 moderate) were still had CD by the 4th PO week. Further, statistical analyses assured the relation between the use of IO DEX infusion and reduction of the incidence and severity of POCD and considered administration of DEX infusion as a positive predictor for maintenance of

CF. These results go in hand with previous studies that assured the efficacy of continuous DEX infusion for alleviating PO pain and reducing anxiety and incidence of POCD [15-20].

Trials to explain the beneficial effect of DEX on CF provided multiple mechanisms, were using a surgical animal model under general anesthesia, DEX was found to effectively improve POCD through reduction of serum levels of interleukin (IL)-1β, 6 and 17A, S-100β and tumor necrosis factor-α (TNF-α) with reduction of expression levels of NF-κB p65 [21], or through inhibiting the Toll-like receptor-4-NFκB signaling pathway in the hippocampus [22] or by promoting degradation of the pyrin-domain containing-3 inflammasome via the autophagy-ubiquitin pathway, and reduced surgery-induced protein expression of caspase-1 and IL-1β, [23].

Clinically, one study found the reduction of incidence of PO delirium on the use of perioperative DEX infusion was associated with PO reduction in circulating levels of IL-6 and stabilization of the hemodynamic profile [15]. Another study detected a significant reduction of serum high-mobility group box 1 protein; a serum neuroinflammatory mediator, with DEX, not placebo infusions [16]. Further, DEX infusion was found to lower serum β-amyloid, TNF-α, IL-1β, and IL-6 in a dose-dependent fashion with a reduction of the incidence of POCD in a parallel manner [24].

The study protocol abandoned the use of an initial loading dose of DEX to guard against excessive hypotension and DEX infusion was used at a rate of 0.5 μg/kg/h and no intraoperative complications were reported, but intraoperative blood loss was significantly reduced. In line with the used infusion rate, a previous study detected a significant reduction in the incidence of POCD; 13.2% vs. 35.8%, with DEX 0.5 μg/kg/h from induction until wound closure compared to placebo infusion [17]. Furthermore, one study compared DEX infusions at rates of 0.2, 0.5, and 0.8 μg/kg/h after a loading dose of 0.3 μg/kg given 10 min before anesthesia induction and found the incidences of POCD with an infusion rate of 0.5 and 0.8 μg/kg/h were comparable and significantly lower than the control group, but the incidences of hypotension and bradycardia were the highest DEX infusion used at a rate of 0.8 μg/kg/hr [24]. Lastly, another study reported that DEX continuous infusion at a dose of 200 or 400 μg significantly decreased the incidence of PO delirium and early POCD after major open surgery in a dose-dependent manner without increasing any side effects [25].

Conclusion

POCD is a frequent post-anesthetic sequela, especially for elderly patients who were exposed to major surgeries of long operative time and predicted blood loss. Intraoperative DEX infusion significantly reduced the incidence of POCD and MMES scores detected throughout the 4-wk PO follow-up duration. The used dose of DEX was appropriate for approaching the target without distressing hemodynamic effects.

Recommendations

Wider scale studies for evaluation of the effect of DEX infusion in patients with evident cognitive dysfunction and to determine its effects on proinflammatory cytokines.

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